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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,593	11/09/2001	Hiroaki Yamamoto	06501-052002	4357

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,593	YAMAMOTO, HIROAKI	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/478163.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 12-32 are pending.

Applicant's amendment of claims 12-18, 20, cancellation of claims 10-11, addition of claims 21-32, and amendments to the specification, in a communication filed on 7/22/2004 are acknowledged.

New claims 21-32 are directed to the subject matter previously examined. Claims 12-32 are under consideration herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 7/22/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the Examiner.

2. Reference AA (Kojima et al.) of the IDS filed on 5/14/2002 has been considered by the Examiner. A copy of this IDS initialed and signed is being forwarded with this Office Action.

Claim Objections

3. Claim 12 is objected to due to the recitation of "wherein activity of the microorganism to regenerate an electron acceptor". For clarity and consistency, the term should be amended to recite "wherein the activity of the microorganism to regenerate an electron acceptor". Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 12-20 remain rejected and new claims 21-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in a previous Office Action mailed on 3/22/2004 and it is applied to new claims 21-32 for the reasons of record and those set forth below.

6. Applicants argue that the specification may satisfy the written description requirement for a given genus without describing every species that the claim encompasses and that whether or nor the written description requirement is met depends upon the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Applicants submit that the genus of oxidoreductases is a recognized class of enzymes, many books have been written about oxidoreductases, many oxidoreductases are known, and that it is the regeneration of the electron acceptor and not the type of oxidoreductase what is the crux of the broadest claims. According to Applicants, information regarding other oxidoreductases would be available to one of skill in the art and is not needed in the specification. It is Applicant's contention that what is claimed is not a compound but a method of using a compound and that one can extrapolate from the specific examples provided in the specification to the broad genus claimed.

7. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection or avoid the rejection of new claims 21-32. The Examiner acknowledges that in order to satisfy the written description requirement, it is not required to describe every species in a genus, however, as discussed in the written description guidelines, the written description requirement for a claimed genus

may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only a few species within the genus.

The genus of oxidoreductases is an extremely large and variable genus encompassing enzymes having different structures, different substrates and different cofactors. While it is agreed that many oxidoreductases are known in the art, it is noted that claims 12-32 are not limited to known oxidoreductases but they also encompass unknown oxidoreductases. Also, while it is agreed that the claimed method requires regeneration of the electron acceptor, the claimed method also requires a microorganism capable of expressing any oxidoreductase which can be grown at low or zero oxygen concentration. As such, the claimed method requires knowledge of (1) any microorganism which produces an oxidoreductase with the functional characteristics recited which can be cultivated at low or zero oxygen concentration, and (2) a polynucleotide encoding any oxidoreductase having the recited functional characteristics such that any microorganism which can be cultivated at low or zero oxygen concentration can be transformed with said polynucleotide. The specification fails to describe (1) the structure which is representative of all the species of the genus of oxidoreductases encompassed by the claims, (2) the structure of the organic compounds/alcohols which can be oxidized by the genus of oxidoreductases recited, (3) the cofactors (electron acceptors) associated with each of the oxidoreductases encompassed by the claims which can be regenerated by cultivating at low dissolved oxygen concentration, (4) the structural characteristics required in any oxidoreductase such that it can

specifically oxidize either the (S) or the (R) enantiomer in racemic alcohol mixtures, and (5) the identity of alcohols which can be oxidized by these enantiomer-specific oxidoreductases and their corresponding electron acceptors. As such, while the claims are directed to a method, in view of the fact that essential information required to practice the claimed method is lacking, one cannot reasonably conclude that the claimed method is adequately described.

Furthermore, while a sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acids sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, in the instant case, there is no recited structural feature. Many structurally unrelated polypeptides are encompassed by these claims. The specification provides one oxidoreductase from C. parapsilosis, one organic compound, and 5 electron acceptors, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed method. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

8. Claims 12-20 remain rejected and new claims 21-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method for oxidizing (S)-1,3-butanediol by contacting (S)-1,3-butanediol with a microorganism capable of expressing the C. parapsilosis alcohol dehydrogenase encoded in pKK-CPA1, wherein said microorganism is cultivated at low dissolved oxygen concentrations, and (2) a method for producing optically active (R)-1,3-butanediol by contacting a racemic alcohol mixture containing (S)-1,3-butanediol with a microorganism capable of expressing the C. parapsilosis alcohol dehydrogenase encoded in pKK-CPA1, wherein said microorganism is cultivated at low dissolved oxygen conditions, does not reasonably provide enablement for (1) a method for producing an oxidized form of any organic compound or alcohol, wherein the method

comprises contacting the organic compound/alcohol with a microorganism whose activity to regenerate any electron acceptor for any oxidoreductase expressed in said microorganism is enhanced by culturing said microorganism at a low dissolved oxygen concentration, or (2) a method for producing any optically active alcohol from any racemic alcohol mixture by using a microorganism capable of producing any oxidoreductase, any C. parapsilosis oxidoreductase, or any alcohol dehydrogenase, wherein said oxidoreductase/alcohol dehydrogenase specifically oxidizes either the (S) or (R) enantiomer in the racemic alcohol mixture, and wherein said microorganism is cultivated at a low dissolved oxygen concentration in order to regenerate any electron acceptor for said oxidoreductase/alcohol dehydrogenase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in a previous Office Action mailed on 3/22/2004 and it is applied to new claims 21-32 for the reasons of record and those set forth below.

9. Applicants argue that the information needed to practice the claimed invention is provided either in the specification or in the art. Applicants submit that other oxidoreductases from other organisms are known in the art and therefore, information regarding these oxidoreductases is not required in the specification. Applicants further argue that the level of skill and predictability in the art is such that detailed schemes are not required for one of skill in the art to practice the full scope of the claimed invention. According to Applicants, all the information required is either explicitly taught in the specification or generally known in the art. Applicants also point out that even if the claims were limited to the alcohol dehydrogenase contained in pKK-CPA1, no biological deposit is required since JP-A-Hei 07-231785 provides information as to how to construct the required vector.

10. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection or avoid the rejection of new claims 21-32. As indicated above in regard to the written description rejection, while it is agreed that several oxidoreductases are known in the art, claims 12-32

encompass a method which uses not only those oxidoreductases known in the art but also unknown ones. The specification is completely silent in regard to the structural elements required in any polypeptide to have oxidoreductase activity, the structure of the organic compounds/alcohols which can be oxidized by any oxidoreductase as encompassed by the claims, (3) the cofactors (electron acceptors) associated with each of the oxidoreductases required by the claimed method that can be regenerated by cultivating at low dissolved oxygen conditions, (4) the structural characteristics required in any oxidoreductase such that it can specifically oxidize either the (S) or the (R) enantiomer in racemic alcohol mixtures, and (5) the identity of alcohols which can be oxidized by oxidoreductases which specifically target a particular enantiomer in racemic alcohol mixtures, and their corresponding electron acceptors. The Examiner disagrees with Applicant's contention that the level of skill and predictability in the art is such that one of skill in the art can practice the full scope of the claimed method. While one could argue that the genus of oxidoreductases required to practice the claimed method can be made/isolated by structural homology using the C. parapsilosis oxidoreductase described in the specification, the art clearly teaches that even highly structurally homologous polypeptides can have different function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Since structure determines function, one of skill in the art would require some knowledge or guidance as to a correlation between structure and the desired function. In view of the lack of information as to how to obtain all the oxidoreductases required, the identity of the organic compounds which can be oxidized, the cofactors which can be regenerated by cultivation at low or zero oxygen concentration, the identity of alcohols which can be oxidized by oxidoreductases which specifically recognize a particular enantiomer in a racemic alcohol mixture and

their electron acceptors, as well as the unpredictability of the art in regard to obtaining proteins of similar function without any clue as to the critical structural elements required in such proteins such that they display the required functional characteristics, one of skill in the art would have to go through the burden of undue experimentation to practice the full scope of the claimed method.

In regard to arguments that a biological deposit is not required for vector pKK-CPA1, since JP-A-Hei 07-231785 provides information as to how to construct the required vector, it is noted that material which is essential to the claimed invention must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. In the instant case, the complete sequence of plasmid pKK-CPA1 has not been disclosed, nor have all the sequences required for its construction been shown to be publicly known and freely available. Therefore, if the claims were to be modified such that they require the oxidoreductase encoded by vector pKK-CPA1, a biological deposit will be required to comply with the enablement requirement. If there is a sequence identifier associated with that oxidoreductase, and the claims were to be amended to refer to that oxidoreductase by its sequence identifier, no biological deposit would be required.

Claim Rejections - 35 USC § 103

11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

12. Claims 10-20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al., Biosci. Biotechnol. Biochem. 63:1051-1055, June 1999) in view of Matsushita et al. (J. Bacteriol. 177:6552-6559, 1995). This rejection has been discussed at length in a previous Office Action mailed on 3/22/2004.

13. Applicants argue that Yamamoto et al. does not expressly identify the level of dissolved oxygen in the media and that the instant reference does not teach or suggest that culturing microorganisms in

media having a low concentration of dissolved oxygen leads to regeneration of electron acceptors, or that manipulating the oxygen levels in the media would be at all effective in increasing such regeneration. Applicants submit that Matsushita et al. fails to cure the deficiencies of Yamamoto et al. because (1) it is well known in the art that E. coli grows better under relative high aeration, and (2) the motivation of Matsushita et al. to carry out experiments at low aeration has nothing to do with regeneration of electron acceptors. Furthermore, Applicants submit that Matsushita's observations are not generally applicable to other oxidoreductases as shown by Applicants in Example 3, where E. coli cells expressing a recombinant oxidoreductase were grown at different levels of aeration and increased activity was found with increasing RPM. Therefore, it is Applicant's contention that the teachings of Matsushita et al. are limited to a particular enzyme and there is no motivation to combine the instant references.

14. Applicant's arguments have been fully considered. While the Examiner agrees that Yamamoto et al. does not teach a correlation between low oxygen levels and increased regeneration of electron acceptors, it is noted that the Examiner relied on the teachings of Matsushita et al., and not those of Yamamoto et al., in regard to the use of low dissolved oxygen concentration to increase the activity of the alcohol dehydrogenase. Furthermore, while it is agreed that E. coli will grow better under aerobic conditions, it is also well known in the art that increased cell mass concentration does not necessarily translate into higher specific enzymatic activity, which is the amount of enzyme per cell (or g cell mass). Thus, if the specific enzymatic activity decreases with increasing cell mass, increasing cell mass may not be the most optimal method to increase enzyme production. In regard to Example 3, it is noted that (1) the oxidoreductase tested is the alcohol dehydrogenase of Yamamoto et al., and (2) increasing RPM does not result in increasing activity as suggested by Applicants. While it is agreed that at 400 RPM, the specific enzymatic activity (U/ml-broth or U/OD) is the lowest, the enzymatic activity is the highest at 600 RPM and decays at 800 RPM. The relationship between RPM and enzymatic activity is not proportional as asserted. Also, it is noted that the correlation shown in Table 1 does not indicate the

dissolved oxygen concentration at the RPM and OD listed, except for 400 RPM (DO = 0). Increasing RPM may not necessarily correspond to an increase in DO since OD is also increasing. Thus, except for the enzymatic activity at 400 RPM (DO=0), the additional values for enzymatic activity cannot be correlated to a DO value. In regard to arguments that Matsushita et al. does not teach that low dissolved oxygen levels lead to regeneration of the electron acceptor, these arguments have been found persuasive to overcome the instant rejection, which is hereby withdrawn.

Double Patenting

15. Applicant is advised that should claim 18 be found allowable, claim 24 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Claim 24 is directed to the same subject matter encompassed by claim 18. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

16. Claims 12-20 remain provisionally rejected and new claims 21-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 40 of copending Application No. 10/147003. This rejection has been discussed at length in a previous Office Action mailed on 3/22/2004. It is applied to new claims 21-32 for the reasons of record as those set forth below.

17. Applicants argue that MPEP 706.02(k) states that when two applications of different inventive entities are co-pending and the filing dates differ, a provisional rejection should be made in the later filed application. According to Applicants, Application No. 10/147003 was filed after the instant application and therefore request withdrawal of the rejection.

18. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 12-20 or avoid the rejection of new claims 21-32. The provisions cited in MPEP 706.02(k) refer to provisional rejections under 102(e)/103 and do not apply to a provisional obviousness-type double patenting rejection. As such, the provisional obviousness-type double patenting rejection applied to claims 12-20 is deemed proper. In addition, newly added claims 21-32 are rejected for the following reasons. Claims 21-22, 25-26, 29-30 are directed in part to a method for producing an oxidized form of an organic compound, wherein the method comprises contacting the organic compound with a microorganism whose activity to regenerate an electron acceptor for an oxidoreductase expressed in said microorganism is enhanced by culturing said microorganism at a dissolved oxygen concentration of 50%, 20%, 10% saturation, or less. Claims 23-24, 27-28, 31-32 are directed in part to a method for producing an optically active alcohol from a racemic alcohol mixture, wherein the method comprises contacting the racemic alcohol mixture with a microorganism whose activity to regenerate an electron acceptor for an oxidoreductase expressed in said microorganism is enhanced by culturing said microorganism at a dissolved oxygen concentration of 50%, 20%, 10% saturation, or less.

As previously indicated, claim 40 of copending Application No. 10/147003 is directed in part to a method for producing (R)-1,3-butanediol, wherein said method comprises producing (R)-1,3-butanediol and 4-hydroxy-2-butanone by oxidizing (S)-1,3-butanediol from a racemic 1,3-butanediol mixture with a microorganism which produces a Candida parapsilosis secondary alcohol dehydrogenase. According to the specification of copending Application No. 10/147003 (page 25, lines 1-13), a preferred embodiment of the invention is practicing the claimed method in combination with an enzyme reaction for regenerating NADH, wherein said regeneration can be obtained by maintaining a low dissolved oxygen concentration. The secondary alcohol dehydrogenase from Candida parapsilosis will oxidize (S)-1,3-butanediol (alcohol) into 4-hydroxy-2-butanone, therefore increasing the concentration of (R)-1,3-butanediol in the racemic alcohol mixture. (R)-1,3-butanediol is an optically active alcohol. As such, new

claims 21-32 are deemed obvious over claim 40 of copending Application No. 10/147003 as it would have been obvious to one of skill in the art at the time the invention was made to practice the claimed method with limitations regarding the % dissolved oxygen concentration as recited in claims 21-32 of the instant application. One of skill in the art would have been motivated to practice the claimed invention at the recited dissolved oxygen concentrations in view of the preferred embodiment disclosed in copending Application No. 10/147003 regarding the low dissolved oxygen concentration required to obtain regeneration of NADH. One of ordinary skill in the art has a reasonable expectation of success at practicing the claimed method at the recited dissolved oxygen concentrations since all that is required is adjustment of the dissolved oxygen concentration during culturing of the microorganism. Therefore, the invention of claims 21-32 would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

19. No claim is in condition for allowance.

20. Applicant's amendment of claims 12-18, 20 and addition of claims 21-32 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
October 4, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600